National Arthritis and
Musculoskeletal and
Skin Diseases Advisory Council

MINUTES OF MEETING

May 23, 2006

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL ARTHRITIS AND MUSCULOSKELETAL AND SKIN DISEASES ADVISORY COUNCIL

MINUTES OF THE 59th MEETING

May 23, 2006
8:30 a.m. to 4:00 p.m.

I. CALL TO ORDER

The 59th meeting of the National Arthritis and Musculoskeletal and Skin Diseases Advisory Council was held on May 23, 2006, at the National Institutes of Health (NIH) Campus, Building 31, Conference Room 10. The meeting was chaired by Dr. Stephen Katz, Director, National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS).

Attendance

Council members present:

Dr. Graciela S. Alarcón
Dr. Kevin Campbell
Dr. Gena R. Carter
Ms. Carmen Cheveres DeMummey
Dr. Lee Green
Dr. Bevra H. Hahn
Dr. Joshua Jacobs (via telephone)
Dr. Brian L. Kotzin
Dr. Martin J. Kushmerick
Ms. Patricia McCabe
Dr. Jack E. Parr
Dr. Lawrence G. Raisz
Dr. Randy N. Rosier
Dr. John R. Stanley
Ms. Sharon F. Terry
Dr. Jouni J. Uitto

Council members not present:

Dr. Robert J. Oglesby (Ex Officio)
Dr. Raymond Scalettar
Dr. Steven L. Teitelbaum

Staff and Guests:

The following NIAMS staff and guests attended:

Staff

Dr. Janet Austin
Dr. Carl Baker
Dr. Michael Bloom
Mr. Gahan Breithaupt
Dr. Eric Brown
Dr. Penny Burgoon
Ms. Anne Connors
Ms. Teresa Do
Mr. Erik Edgerton
Mr. Raymond Fleming
Ms. Valerie Green
Dr. Elizabeth Gretz
Dr. Steven Hausman
Ms. Megan Hylton
Ms. Jane Hymiller
Dr. Stephen Katz
Ms. Julaine King
Dr. Cheryl Kitt
Dr. Gayle Lester
Dr. Helen Lin
Dr. Joan McGowan
Ms. Leslie McIntire
Ms. Sherry Meltzer
Mr. Robert Miranda-Acevedo
Ms. Melinda Nelson
Dr. Glen Nuckolls
Dr. John O'Shea
Dr. James Panagis
Ms. Wilma Peterman
Ms. Karin Rudolph
Dr. Susana Serrate-Sztein
Dr. William Sharrock
Dr. Lawrence Shulman
Ms. Sheila Simmons
Ms. Helen Simon
Ms. Robyn Strachan
Mr. Yen Thach
Mr. Michael Toland
Dr. Madeline Turkeltaub
Dr. Bernadette Tyree

Dr. Yan Wang

Guests

Dr. Zohara Cohen, National Institute of Biomedical Imaging and Bioengineering, NIH
Ms. Deborah Deitz, SSS
Ms. Ann Elderkin, American Society for Bone and Mineral Research
Ms. Bonnie Ellis, Division of Extramural Activities Support, NIH
Ms. Christy Gilmour, American Academy of Orthopaedic Surgeons
Ms. Leslie Hanrahan, Lupus Foundation of America
Mr. Bob Jasak, American Academy of Orthopaedic Surgeons
Ms. Darlene Kerr, Circle Solutions
Ms. Patti Brandt Hansberger, Office of Legislative Policy and Analysis, NIH
Ms. Hilary Hansen, National Psoriasis Foundation
Ms. Jennifer Love, Division of Extramural Activities Support, NIH
Dr. Teri Manolio, National Human Genome Research Institute, NIH
Dr. Cheryl Oros, Center for Scientific Review, NIH
Ms. Shelly Pollard, Office of the Director, NIH
Ms. Elizabeth Rivera, Lupus Foundation of America
Ms. Dana Thigpen, Center for Scientific Review, NIH
Ms. Susan Whittier, National Osteoporosis Foundation
Ms. Carolyn Williams, Office of Equal Opportunity and Diversity Management, NIH
Ms. Sandy Williams, Office of the Director, NIH
Ms. Roxanne Yaghoubi, Society for Investigative Dermatology
Dr. Elias Zerhouni, Director, NIH

II. CONSIDERATION OF MINUTES

A motion was made, seconded, and passed to accept the minutes of the 58th Council meeting, held on January 17, 2006.

III. FUTURE COUNCIL DATES

Future Council meetings are currently planned for the following dates:

September 26, 2006
February 27, 2007
June 12, 2007
September 27, 2007
January 29, 2008
May 27, 2008
September 23, 2008

IV. DIRECTOR'S REPORT AND DISCUSSION

Dr. Katz welcomed the members of the Council and noted that NIAMS is celebrating its 20th anniversary. One component of this celebration involves releasing a series of articles focusing on the progress that has been made in each area of the Institute since its inception in 1986.

Dr. Katz introduced Dr. Bevra Hahn, Professor of Medicine, Chief of the Division of Rheumatology, and Vice Chair for Faculty Affairs in the School of Medicine, University of California, Los Angeles. Dr. Hahn participated in her first meeting as a member of the Council by conference call.

Personnel Changes

Dr. Katz announced that this was the last Advisory Council meeting for Dr. Cheryl Kitt, Director of the NIAMS Extramural Program and Council Executive Secretary, and thanked her for the many contributions she has made to NIAMS over the years. Dr. Kitt is moving to the NIH Center for Scientific Review, where she will serve as Deputy Director.

Dr. Madeline Turkeltaub, who serves as the NIAMS Extramural Program's Clinical Research Project Manager and Manager of the Office of Research on Women's Health Specialized Centers of Research Program, has accepted the position of Deputy Director of the NIAMS Extramural Program.

Dr. Deborah Ader, Program Director, Rheumatic Diseases Branch for Behavioral and Prevention Research, has left NIAMS for to pursue an opportunity in the private sector.

As was announced at the last meeting, Dr. Alan Moshell has retired from NIAMS. Dr. Carl Baker, who has a wealth of experience in the field of skin diseases, has taken over the management of Dr. Moshell's skin diseases research portfolio.

Update on Budget and Congressional Activity

Within the fiscal year (FY) 2007 President's Budget, the NIH program level is $28.6 billion—essentially the same as the post-rescission level for FY 2006. The total FY 2007 budget for NIAMS is $504.5 million, which includes funds to be transferred for NIH Roadmap activities; this is a reduction of 0.7 percent from the FY 2006 level. NIAMS has taken a number of steps to preserve the Institute's success rate and payline to the greatest extent possible, including revised policies for program project grants, administrative reductions, and the utilization of accelerated funding activities from FY 2002 and FY 2003. At this time, it is expected that the success rate for FY 2007 will be approximately 16 percent for NIAMS compared to 19 percent for NIH as a whole. It is likely that NIAMS' success rate for FY 2006, which will be calculated at the end of December, will be close to 19 percent compared to the NIH estimate of approximately 20 percent.

The House Appropriations Subcommittee on Labor, Health and Human Services (HHS), and Education held its overview of the FY 2007 President's budget for NIH on April 6, 2006. Dr. Elias Zerhouni, Director, NIH, testified on behalf of the NIH. A large number of written

questions for the record were received, including queries about lupus, psoriasis, osteoporosis, and health disparities.

Dr. Zerhouni also testified at the May 19, 2006, Senate Appropriations Subcommittee on Labor, HHS, and Education's overview of the FY 2007 President's Budget. Although Dr. Katz did not provide verbal testimony at these hearings, his written statement is available on the NIAMS Web Site.

Highlights of Recent Scientific Advances

- The results of the Glucosamine/Chondroitin Arthritis Intervention Trial (GAIT) were recently published in *The New England Journal of Medicine*. This 4-year study of approximately 1,600 participants found that the dietary supplement combination of glucosamine and chondroitin sulfate did not provide all participants with significant relief from osteoarthritis pain. However, a subgroup of participants with moderate to severe pain did experience significant levels of pain relief. An evaluation of the effect of these agents on the progression of osteoarthritis, including joint space narrowing, among a smaller group of participants is ongoing.

- The Women's Health Initiative Study has found that calcium and vitamin D supplements in healthy postmenopausal women modestly benefit the preservation of bone mass and the prevention of hip fractures in certain groups, including older women. The supplements were not found to prevent other types of fractures or colorectal cancer. Although generally well tolerated, the supplements were associated with an increased risk of kidney stones. This paper, coauthored by Dr. Joan McGowan, Director of NIAMS' Musculoskeletal Diseases Branch, was published in the February 2006 issue of *The New England Journal of Medicine*.

- Dr. Melissa Spencer, recipient of a Presidential Early Career Award for Scientists and Engineers, and her colleagues have discovered the role of genetic mutation in two forms of muscular dystrophy. This NIAMS-supported research project uncovered a possible mechanism through which interference with one aspect of normal muscle turnover results in the development of limb-girdle muscular dystrophy type 2H and sarcotubular myopathy.

- NIAMS-funded researcher Dr. Richard Wenstrup and his colleagues at the Cincinnati Children's Hospital Medical Center have found a potential approach to treating the devastating genetic bone disease osteogenesis imperfecta (OI). The most common cause of OI is a defect in the gene that controls the production of Type 1 collagen proteins. In severe cases, this results in both the production of insufficient amounts of collagen and the production of defective collagen. The defective collagen interacts with other proteins, magnifying the defect's harmful effects. The challenge is to find a way to reduce or eliminate the production of the defective protein without affecting the same cells' production of normal collagen. In this study, specially designed ribozymes that act as molecular scissors were developed to cut off communication between the defective gene and collagen-producing cells.

- Dr. Donald Leung of the National Jewish Medical and Research Center in Denver, Dr. Richard Gallo of the University of California, San Diego, and colleagues have identified a defect in the immune response of people with the skin condition atopic dermatitis that puts them at risk of developing serious complications following smallpox vaccination. The study, supported by NIAMS and the National Institute of Allergy and Infectious Diseases (NIAID), used laboratory-grown human skin cells to show that an immune system protein called LL-37 is critical in controlling the replication of vaccinia virus, the live virus in the standard smallpox vaccine. Atopic dermatitis patients lack this protein, so their keratinocytes are easily infected by the vaccinia virus.

- Dr. Harry Dietz of Johns Hopkins, Dr. Francesco Ramirez of the Hospital for Special Surgery in New York, and colleagues have shown that in mice designed to develop manifestations of Marfan Syndrome, aortic aneurysms can be prevented with the use of angiotensin Type II receptor blockers. This is a very important advance because ruptured aneurysms are what make Marfan Syndrome fatal. This drug is on the market and is ready to undergo clinical trials testing.

- Within the NIAMS Intramural Research Program, Dr. Daniel Kastner, Chief of NIAMS' Genetics and Genomics Branch, and colleagues have shown that anakinra, an IL-1 receptor antagonist, is a very efficacious treatment for neonatal onset multisystem inflammatory disease.

- At the University of Pennsylvania, Dr. Fred Kaplan and colleagues have shown that a recurrent mutation in the Bone Morphogenetic Protein (BMP) Type I receptor ACVR1 causes inherited and sporadic fibrodysplasia ossificans progressive, a spectrum of diseases that causes some children to become encased in muscle embedded with bone. This finding provides a real target for intervening in this devastating disorder.

Highlights of Recent Activities

A booklet exploring the role of bones, muscles, and skin that NIAMS prepared as an educational tool for 7th and 8th graders is in the process of being distributed across the country. A presentation on this curriculum was made at the June 14, 2005, Council meeting.

On May 8-9, 2006, NIAMS sponsored a very successful meeting, titled The Genetics of Bone Mass and Fracture Risk in Humans. Dr. William Sharrock, Program Director for the Bone Biology Program in the Musculoskeletal Diseases Branch, NIAMS, will provide the members of the Council with a report on this meeting.

The NIAMS Extramural Program held its annual scientific retreat on April 24-25, 2006. Dr. Martin Kushmerick, Professor in the Department of Radiology at the University of Washington and a member of the NIAMS Advisory Council, will provide a brief report on the retreat, later in this meeting.

V. NIH AT THE CROSSROADS: MYTHS, REALITIES, AND STRATEGIES FOR THE FUTURE

Dr. Zerhouni thanked the members of the Council for their service, noting that NIH makes decisions on the basis of the input it receives from more than 31,000 scientist advisors each year.

The following environmental factors have had a significant impact on the NIH budget:

- Federal and trade deficits
- Defense and Homeland Security needs
- Hurricane Katrina
- Pandemic flu response
- Post-doubling effects
- Increased focus on the physical sciences
- Biomedical research inflation rates of 3 to 5 percent.

The NIH Roadmap for Medical Research, which was developed to increase synergy across the NIH, represents a small portion of the annual budget. In FY 2005, Roadmap funding supporting more than 345 projects accounted for 0.8 percent of the total NIH budget.

Dr. Zerhouni reported that three fundamental factors drive the current NIH budget:

- Large capacity building activities at U.S. research institutions, including an increase in the number of tenure-track faculty members.
- A large increase in the number of grant applicants and applications since 2003.
- Budget appropriations levels that have been below inflation levels since 2003. This problem is compounded by the impact of the budget cycling phenomena: at NIH, only a small percentage of the annual budget is a reflection of year-to-year increases because the vast majority of the budget is committed to the funding of ongoing and soon-to-end grants.

In addition, over the past 2 years there have been almost as many new applicants as there were in the previous 5 years. (There were 5,334 applicants between 1999-2003, and 5,208 applicants between 2003-2005.)

The bottom line is that the demand for NIH grants accelerated at the same time that the NIH budget began to level off. Dr. Zerhouni noted that in FY 2004 and FY 2005, NIH was able to compensate by shifting "one time" funds from FY 2003 to FY 2004 and by obtaining small

increases in FY 2004 (2.9%) and FY 2005 (2%) funding. As these funds were not available for FY 2006, the NIH budget remained flat while the rest of the Department of Health and Human Services underwent a 2.5 percent budget cut.

In FY 2007, the budget cycling situation will result in improved demand versus supply of grants. Nonetheless, if future biomedical research is to continue at a steady pace, the public must be educated about the need for sustainability in research.

It also is important to remember that: (1) the NIH grant success rate is higher than the percentile payline, and (2) the success rate for applicants (approximately 25% in FY 2006) is always higher than that for applications (19% in FY 2006).

Dr. Zerhouni noted that the Federal Government is the only real source of support for basic discovery and research in the United States, and only one-third of the federal research and development budget—$28 billion—goes to NIH. Pharmaceutical and biotechnology firms spend $56 billion per year on research and development, most of which is applied. It is important for NIH to continue its investment in basic discovery, but this needs to be accomplished through a balanced research portfolio.

As he looks to the future, Dr. Zerhouni plans to:

- Develop adaptive strategies designed to protect the essential elements of knowledge and discovery, increase the number of competing grants (through supply/demand management), and support new investigators via the new Pathway to Independence Program and Institute and Center efforts to assist new investigators.

- Increase communications to local, regional, and national audiences about the benefits that accrue from NIH-funded activities. For example, Americans are living longer and healthier lives because of improvements in recovery from heart disease and stroke, deafness, vision impairment, osteoporosis, and bone and joint health. As a result, since 1982, the disability rate for elderly Americans has declined by 30 percent. Dr. Zerhouni asked for the Council's help in educating Congress, local government leaders, and the public about what the funds invested in NIH accomplish both in terms of advances in public health and on the impact research funding has on employment and other aspects of the local economy.

NIAMS Council member Dr. Jack Parr, Consultant, Medical Technology Development, Inc., pointed out that over the last several years the Whittaker Foundation has directed about $600 million to biomedical engineering and biomedical research departments and efforts to train researchers in these areas. This activity may well have had an impact on the increases seen in the number of NIH applicants. Dr. Parr also suggested that from a public relations perspective, it would be helpful to provide specific concrete examples of clinical successes before describing NIH accomplishments in more general terms.

Dr. Lawrence Raisz, Council member and Director of the University of Connecticut Center for Osteoporosis, inquired about the status of the Senate recommendation for increasing the NIH FY

2007 budget. Dr. Zerhouni replied that the Senate has proposed an addition of $2 billion to NIH's FY 2007 funding level. On the House side, efforts have been made to shift funds from other agencies to HHS and NIH. However, he does not expect a definitive answer to this question until the end of 2006 (after the fall elections).
In response to a question from Dr. Raisz about the impact the Clinical and Translational Science Award (CTSA) Program will have on the number of General Clinical Research Centers (GCRCs), Dr. Zerhouni indicated that he believes that the more tightly focused and consolidated GCRC Program actually will grow by 50-60 percent. However, increased emphasis is being placed on translational science. Accordingly, the total number of GCRCs will be influenced by budget levels and the quality of the proposals received.

Dr. Kushmerick indicated that it would be beneficial if NIH could more clearly explain the budget situation to investigators with scores above the payline whose grants are not funded.

Council member Dr. John Stanley, Chairman of the Department of Dermatology at the University of Pennsylvania School of Medicine, agreed with Dr. Zerhouni's concern regarding supply and demand. Is it always advisable to encourage new investigators to seek grants? Is there a more creative way to determine who should pursue research? Should alternate career paths be offered? Although a high-level competition is good for science, it is not always good for the people involved. Dr. Zerhouni replied that the key issue is determining the appropriate number of investigators. There are roughly 50,000 postdocs under RO1-type grants, some of whom are not truly independent scientists; rather, their work supports the research activities of complex organizations. On the other hand, if new investigators are not encouraged and a large number drop out, the pool of available talent may be insufficient when more funding becomes available. Demographics also are important: current projections estimate that 33 percent of scientists will retire in the next 3 to 5 years; this figure will jump to 50 percent in 5 to 10 years.

Council member Dr. Kevin Campbell of the University of Iowa Carver College of Medicine asked why the NIH places such a large emphasis on the number of proposals rather than productivity as measured by the number of publications generated. Dr. Zerhouni replied that for many researchers, scientific publications are an insufficient measure of potential talent. He agrees that NIH needs to move away from an overly bureaucratic focus on applications and toward measures of performance; the question is how to do so.

Ms. Patricia McCabe, patient advocate with the National Marfan Foundation and member of the Advisory Council, agreed that it is important to educate the public about the role and impact of NIH. During her 12 years with the National Marfan Foundation, she has seen a decrease in knowledge about NIH and how it pertains to the work of her organization. How can patient advocacy groups partner with NIH to help get the message across to their membership? Dr. Zerhouni indicated that one major problem is that people underestimate how long it takes for a fundamental discovery to become an actual application; it also is difficult for the public to grasp how hard it is to understand the complexities of biological systems.

Dr. Bevra Hahn commented on the need for NIH or other support to train clinical investigators who are independent of the influences of pharmacological companies. Dr. Hahn would like to see a Pathway to Independence-type program for M.D. researchers because she believes that

over the next 2-3 years, there will be a huge drop off in the number of M.D. researchers. Drs. Katz and Zerhouni explained that the Pathway to Independence Program is intended for individuals exhibiting the most potential for research, regardless of the type of degree. Dr. Raisz pointed out that in most U.S. medical schools, tenure track positions are not given to clinical investigators—this makes them ineligible for inclusion in the Pathway to Independence Program. Dr. Katz replied that this is a good example of how NIH is working to change the paradigm. To take advantage of NIH programs and encourage the scientific careers of those who are likely to be successful, universities and academic health centers will need to make changes. Dr. Zerhouni added that this also is the essence of the concept behind the CTSA Program, to create an academic home with career- and tenure-track potential.

VI. WHOLE -GENOME ASSOCIATION STUDIES AT NIH: OPPORTUNITIES FOR PARTNERSHIPS

Dr. Teri Manolio, Senior Advisor to the Director for Population Genomics, National Human Genome Research Institute, described the opportunities for partnerships that have been generated by the NIH Whole-Genome Association Studies. She noted that her perspective is based on her experience with the National Heart, Lung, and Blood Institute (NHLBI), the Genetic Association Information Network (GAIN), and the Genes and Environment Initiative (GEI).

Several major NHLBI cohort studies have investigated large numbers of people for 10 to 50 years. The disadvantages to such studies are that they are expensive, take a long time, and are very broad based. The advantages of these cohorts are that they provide risk information that cannot be obtained by any other means, identify modifiable risk factors for potential preventive interventions, are understandable to the public, and provide a rich resource for secondary analysis or additional measures of exposures and outcomes.

Dr. Manolio urged the NIAMS research community to consider ways to build on existing cohort studies and clinical trials, noting that it is relatively inexpensive to add risk factor and outcome assessments to ongoing studies. Osteoporosis outcome measures are increasing with dual energy X-ray absorptiometry (DEXA) and coronary calcium scanning, and arthritis outcomes already are a component of the Framingham Study. In addition, the availability of whole-genome association (WGA) genotyping makes multiple uses even more compelling.

In terms of data access, NHLBI's large population studies are required to prepare de-identified data sets 3 years after an individual is examined; earlier release of WGA data has been proposed. Open access to data is available only to investigators with Institutional Review Board (IRB) approval who agree to established policies. A distinction also is made between the use of data sets for commercial and non-commercial purposes on the basis of participant consent.

Dr. Manolio noted that more efficient association studies could be conducted if investigators focused solely on the density of single nucleotide polymorphisms (SNPs) needed to find associations between SNPs and diseases, targeted chromosomal regions associated with disease, and used this information to produce a tool to assist efforts to find genes affecting health and disease. Consideration also should be given to differences in the degree of linkage disequilibrium found in ancestral populations. For example, because recent African ancestry

populations are older and have shorter stretches of linkage disequilibrium, more SNPs are required for complete genome coverage of these groups.

GAIN is a public-private partnership of the Foundation for NIH, Inc., that will use samples from existing studies to conduct a series of whole genome association (WGA) studies. The project is expected to contribute to the identification of genetic pathways that cause or raise susceptibility to disease, and the resulting data will be freely accessible to members of the scientific community. Those using the data must agree that they will not violate the confidentiality of the parties involved or seek to patent the outcome of their work.

GAIN will invite investigators in existing studies to submit samples and data (with personal identifiers removed) on 800 to 1,000 persons with disease and an appropriate number of disease-free controls for WGA genotyping. Projects will be selected for genotyping on the basis of the strength of evidence that the disease has a genetic component, the public health significance and complexity of the trait, the estimated power to detect a genetic effect, the quality of the DNA and phenotypic/exposure data, and the appropriateness of the study design and population. The deadline for GAIN applications was May 9, 2006, and the first data set is expected to be made available in January 2007.

The NIH Office of Human Research Protections has ruled that GAIN does not involve research on human subjects; therefore, IRB oversight will occur solely at the investigator level. User requests will be reviewed by a Data Access Committee, and a Data Protection and Participant Monitoring Board will assess how data are used over time.

Dr. Manolio provided the members of the Council with an overview of the GEI. The Initiative, proposed in the President's budget for FY2007, aims to accelerate understanding of genetic and environmental contributions to health and disease by: (1) genotyping case-control studies of common diseases; and (2) developing innovative technologies with which to measure environmental exposures, diet, and physical activity.

The GEI seeks to facilitate rapid access to data from large population studies, take advantage of the increasing sophistication of information systems and their users, and encourage the participation of investigators possessing novel insights and perspectives.

The Initiative's genetics component proposes the utilization of the GAIN database and the development of NIH-wide policies for data sharing. Planners anticipate the incorporation of multiple components such as WGA genotyping, replication and fine mapping, sequencing, functional studies, clinical translation, state-of-the-science data analyses, and bioinformatics/database management support.

Dr. Manolio reviewed the evolution of the data-sharing policies of the scientific community, noting the many benefits generated by open access. On May 15, 2006, a Notice to Applicants for NIH Genome-Wide Association Studies was released to inform investigators of NIH plans to:

- Update data-sharing policies for research applications involving genome-wide association study (GWAS) data.

- Initiate a public consultation process that will inform the development of new policies in this area.
- Track GWAS applications and awards at a central level.

Council member Dr. Jouni Uitto, Chair of the Department of Dermatology and Cutaneous Biology at Jefferson Medical College, referred to the recent Centers for Disease Control and Prevention (CDC) announcement on genetic linkage to chronic fatigue syndrome, the validity of which has been criticized because of limited SNP size and the small size of the cohort. How does this contrast to the rigor of the NHLBI studies? Dr. Manolio replied that she is not familiar with the CDC study and would need to look into it before making a comparison. Usually, the problem lies within the selection process and what comparison group is used. It also is important to be wary of efforts by the media and others to trumpet findings that are not strong and robust. In the end, the proof is in the ability to reproduce findings in other cohorts; the design of GAIN and GEI will allow this to be done very quickly.

Dr. Brian Kotzin, Vice President of Global Clinical Development, Amgen, and a member of the Advisory Council, asked how the studies will address the issue of false positives. Dr. Manolio indicated that although GAIN is only funding initial studies, applications are being judged on the basis of their plans for replication. The GEI is hoping to go beyond that by encouraging investigators to include plans for both an initial scan and a replication study in their applications.

Dr. Raisz pointed out that there is a linkage disequilibrium between genotypers and phenotypers. How will GAIN and GEI deal with the shortage of people who are capable of conducting the clinical analysis and phenotyping of multigenic diseases? Dr. Manolio agreed that this is an enormous problem and welcomed the Council's input on the issue. She noted that the staff and peer reviewers for GAIN and GEI have been asked to try to make the phenotype definition as clear, standardized, and comparable across studies as possible. In addition, the analysis workshops for the projects will seek input from experts who know how to analyze the data and define these syndromes.

Dr. Kotzin asked if the GAIN and GEI planners had discussed the possibility that this effort would have a negative effect on the use of other approaches. Different strategies would be needed, for example, in the case of very rare alleles that are only found in specific populations. Dr. Manolio replied that although this is one of the reasons GEI was designed to be more than a WGA, it is most likely that families—not populations—will be the focus of efforts to study rare alleles.

Ms. Carmen Ceveres DeMummey, patient advocate and Council member, asked about the number of applications received as compared to the number that will be funded. Dr. Manolio confirmed that a gratifying number of GAIN applications had been received, of which funding is available for seven. The Foundation for NIH also is actively seeking additional funds from advocacy groups, foundations, and the pharmaceutical industry. The GEI will target another 12 to 15 diseases.

VII. GENETICS OF BONE MASS AND FRACTURE RISK IN HUMANS MEETING REPORT

Dr. William Sharrock, Bone Biology Program Director, Musculoskeletal Diseases Branch, NIAMS, reported on the Genetics of Bone Mass and Fracture Risk in Humans meeting sponsored by the Institute and held May 8-9, 2006.

This meeting, the first in a series, was convened to explore innovative, collaborative ways to apply genomic advances to research targeting bone diseases. Participants included key researchers of clinical cohorts currently being investigated with NIAMS and/or National Institute on Aging support.

Dr. Sharrock noted that previous, mostly family-based studies that looked for genetic linkages associated with bone mass and fracture risk have not been particularly successful. Their findings indicate that numerous genes are involved and the effects of any one gene are relatively small. The question is: would combining cohorts, sharing resources, and collaborating in analysis activities help? How should the bone community take advantage of current GWA initiatives?

With this in mind, the participants engaged in extensive roundtable discussions focusing on:

- A review of existing clinically characterized cohorts. They are numerous, some are quite large, and some cohorts have been intensively clinically characterized over long periods of time. The resources on the phenotypic side, therefore, appear to be substantial.

- The phenotypes measured. The clinical standard is bone mineral density (BMD) as determined by DEXA; other studies have tracked fracture incidence and used more recently developed techniques such as computerized tomography (CT) to estimate bone mass. Other efforts have used X-rays or CT data to try to develop reflections of bone architecture.

- The cohorts that have conducted genotyping. The largest studies, however, were designed along traditional epidemiologic lines, not to conduct genetic analysis. Some of these studies did store DNA or blood that could be adapted to genotyping efforts.

- Practical problems and models that could be applied to efforts to engineer collaborations, consortia, or shared resources. The challenges faced include:

  - Assuring the consistency of clinical measurements. Does BMD mean the same thing when it has been assessed at different sites, in different populations, and with different instruments? Collaborative use of CT data also will present problems of normalization.

  - Questions associated with analytical design. Is the case-control model appropriate for osteoporosis? BMD is a continuously variable trait. In linkage designs, it has been assessed as a quantitative trait locus—very different from the case-control dichotomy. Some argue that a case-control approach could be used that compares osteoporotic

fracture to nonfracture. However, many in the community feel this is not valid because knowing that a person has not fractured yet does not confirm that the individual will not suffer a future fracture.

- What type of consent have cohort participants given? Is it adequate for the comprehensive genotyping activities proposed?

- Addressing the strong sense of ownership investigators have for their clinical cohorts. How should credit be apportioned? What controls would be in place? Existing consortia have carefully constructed rulebooks defining who has access to what and when, who will be an author on resultant papers, etc.

Dr. Sharrock observed that over the course of the 1.5-day meeting, the views of most participants shifted away from a focus on obstacles toward an appreciation of the valuable opportunities the proposed collaboration has to offer. The next step is to convene a second meeting that will hone in on the most critical issues, collect additional information on available cohorts, include additional participants not involved in the initial meeting, and develop a practical approach for implementation.

Dr. McGowan noted that investigators are concerned about what will happen when the results of these types of collaborative projects have been made public. Will the phenotypers and genotypers who have been involved with the GAIN, GEI, and bone mass and fracture risk cohorts be able to obtain funding with which to investigate the mechanisms identified, new pathways, and pathophysiology of these disorders? This issue needs to be addressed and communicated to the NIH research community.

VIII. OPEN ACCESS POLICY

Dr. David Lipman, Director of the National Center for Biotechnology Information (NCBI), National Library of Medicine (NLM), reported on the status of the NIH open access policy, the goal of which is to provide health professionals and the public with electronic access to NIH-funded research publications, create a central archive of NIH-funded research publications, make it easier for people to mine research publications, and help NIH better manage its research portfolio.

There has been a linear increase in the number of papers posted annually on PubMed/MEDLINE since 1967. Over the past decade, however, the number of biomedical databases has grown exponentially. Data usage also is increasing rapidly, and today's researchers are using and generating more data per paper than ever before. In April 2006, approximately 2 million users downloaded more than 3.1 terabytes of data from NCBI each day.

PubMed Central was created in 2000 to provide an archive of biomedical publications. Articles from as far back as the 1870s were scanned and added to the system. PubMed Central directs users to multiple sources of information and provides convenient links to other sites such as PubChem. During April 2006, approximately 5 million users accessed PubMed Central.

However, most users don't have a sufficient understanding of how they can best mine the site, so NCBI is developing the equivalent of an advertisement to disseminate this information.

Congress requested that NIH develop an open access policy in 2003/2004. The policy took effect in 2005, with the implementation of the NIH Manuscript Submission (NIHMS) system, which requests (not requires) that manuscripts describing NIH-funded research be made available to NLM within 12 months.

Dr. Lipman noted that the NIHMS system is working efficiently and within budget estimates. Although the system offers a special process for publishers who want to submit on behalf of their authors, publishers have been incongruent in their positions on submitting articles. Surveys have indicated that most authors are aware of NIH's open access policy; however, less than 4 percent of eligible articles are being submitted. These rates, typical of a voluntary approach, also reflect the fact that most authors are unclear about the requirements of their copyright transfer agreements with their publishers.

In May 2005, the NLM Board of Regents established a Public Access Working Group representing all stakeholders—researchers, publishers, scientific societies, librarians, disease advocacy organizations, and the general public. On the basis of the Working Group's discussions, the Board forwarded the following recommendations to Dr. Zerhouni in February 2006:

- The deposit of articles in the NIHMS system should be mandatory.
- It would be highly desirable for the article submitted to be the final, edited, and published version.
- Public access to the contents of the article should be available within 6 months of publication, with extensions of up to 12 months in a few special cases.

In January 2006, NIH provided the House and Senate Appropriations Committees with a report on the status of the open access policy. In addition, two pieces of pending legislation reflect Congress' continued interest in this issue:

- The CURES Bill, introduced in December 2005, directs U.S. Department of Health and Human Services grantees to provide PubMed Central with an electronic copy of the final version of all peer-reviewed manuscripts accepted for publication within 6 months of publication.
- The May 2006 Federal Research Public Access Act, which applies to all Federal agencies with extramural research expenditures of more than $100 million, requires the submission of an electronic version of the author's final manuscript of original peer-reviewed research papers accepted for publication; free online public access to the manuscripts should be available no later than 6 months after publication.

Dr. Lipman concluded with a review of the following related activities:

- In the United Kingdom, the Wellcome Trust Policy and the Arthritis Research Campaign both mandate that articles be deposited into a public access database within 6 months of publication. The British Heart Foundation is expected to begin following this policy in the next few months.

- The Scottish Health Department's Chief Scientist Office requires that manuscripts be deposited into a public access database within 6 months of publication.

- An Association of Learned and Professional Society Publishers survey of libraries found that public access was not a significant factor in decisions regarding journal subscriptions.

- A May 2006 Public Library of Science article showed the importance of open access to the public and the research community.

In response to a question from Dr. Katz about what should happen next, Dr. Lipman stated that he felt that all NIH-funded articles should be posted to the NIHMS system within 6 months of publication. This would not hurt the publishers and would make a large amount of valuable information available to those who need it.

Dr. Hahn asked why another database is needed when PubMed already is available. Ms. Sharon Terry, President and Chief Executive Officer of the Genetic Alliance and a member of the Advisory Council, replied that PubMed only provides a citation, not the full paper. Dr. Lipman noted that a centralized site is vital to ensuring the long-term viability of information that is difficult to pull together from different sites.

In response to a question about implementation, Dr. Lipman stated that if submissions were mandatory, nonprofit organizations could be expected to coordinate submissions to PubMed Central. Publishers are moving toward a service-based approach, and it would make sense for them to apply this approach to peer-reviewed articles.

IX. NIAMS EXTRAMURAL PROGRAM SCIENTIFIC RETREAT REPORT

Dr. Kushmerick provided the Council with an overview of the reports and discussions at the April 25-25, 2006, NIAMS Extramural Program Scientific Retreat.

The topics addressed at the Retreat included genetic association and genotyping, the basic biology and therapeutic use of stem cells, tissue regeneration and development, roadblocks, and landmark accomplishments to celebrate in conjunction with the 20th anniversary of NIAMS.

In the area of genetic association studies, participants determined that genotyping of individuals is a reality. Although genotyping is the preferred way to deduce causal mechanisms (as opposed to apparent linkages), too few statistically competent geneticists have been trained to do work in this area. Issues associated with data collection include data management and security,

mechanisms for sharing data, and ethics. The attendees also discussed the new GAIN and GEI programs described by Dr. Manolio.

Retreat participants reviewed the enormous potential of stem cells, including keratinocyte stem cells, muscle-derived stem cells (that differ from satellite cells), and pericytes in endothelium, noting that a critical mass of science within NIAMS is needed to adequately pursue the opportunities in this field. There also is a need for markers that can identify stem cells; although stem cells can be permanently marked to detect future progeny, a means for detecting such cells in humans is lacking. The expansion of cell mass in culture is limited by the changes that occur in the cells. Local effects are critical because the environment in which a stem cell finds itself has a major influence on what it does.

In the area of regeneration and development, the attendees determined that there is an enormous need for musculoskeletal and skin tissue regeneration following trauma and surgery. Current tools that are useful for engineering tissues include BMP, TGFβ , Wnt, βcatenin, VEGF, and noggin. Muscle-derived stem cells and gelforms also aid in healing skeletal defects. There is a critical need for further information on the role of cellular and tissue structure (architecture). Expertise from the fields of systems biology, engineering, and biology should be integrated into these efforts, and the interactions between signal molecules also need to be identified.

In terms of roadblocks, the participants noted that there are issues in the areas of data sharing, patient confidentiality, and intellectual property. The importance of systems thinking also was emphasized. Cultural values have a major impact on scientists, academics, and pharmaceutical company employees, and any effort to influence behaviors must take these influences into account.

Dr. Kushmerick concluded with the following insights:

- A radical revision of clinical and basic science training practices is needed that will: (1) treat medicine as an information science; (2) fully integrate the fields of physics, chemistry, engineering, and biology; and (3) utilize simulation and quantitative, mechanistic modeling.

- The cost/benefit analysis of NIH programs should be made clear to researchers. Within the scientific community, feelings of anger and distrust have been caused by the perception that new programs are limiting investigator-initiated opportunities.

Dr. Joshua Jacobs of RUSH University Medical Center and a member of the Advisory Council, who participated in the Retreat, indicated that Dr. Kushmerick had done an admirable job of presenting the points discussed. Dr. Jacobs described the attendees' concerns about manpower issues, particularly the shortage of statistical geneticists and the lack of sufficient genetic expertise on research teams. He also noted that despite tremendous opportunities in the area of musculoskeletal regeneration, obstacles presented by the regulatory entities have prevented basic scientific advancements from becoming clinical applications. Dr. Jacobs would like to see improved collaborations between NIH and the U.S. Food and Drug Administration to help alleviate this problem.

Dr. Gena Carter, Radiologist, patient advocate, and Council member, noted that she sees a critical need for targeted molecular therapies that appear to be a long way from being implemented. Dr. Katz pointed out that work on molecular targeting is taking place in the fields of stem cell research and regenerative medicine.

X. NIAMS LONG-RANGE PLAN UPDATE

Dr. Penny W. Burgoon, Science Policy Fellow at the Office of Science Policy and Planning, NIAMS, and Dr. Katz provided an update of the NIAMS Long-Range Plan. The purpose of the Plan is to guide—but not dictate—NIAMS funding, enhance communications with the scientific community, and indicate where the Institute is heading. The updated Plan covers the time period of FY 2006 to FY 2009.

The draft Long-Range Plan was developed with input received from long-range planning meetings and NIAMS scientific staff. On March 24, 2006, an invitation to comment on the Plan was forwarded to members of the NIAMS Coalition and Institute grantees and posted on the NIAMS Web Site. The comments received suggested the inclusion of additional information on health disparities, training objectives, and partnerships with other NIH Institutes. It also was suggested that the Plan be made more user friendly.

NIAMS staff members are currently incorporating these suggestions into the final draft of the Long-Range Plan, the general contents of which will remain unchanged. The final Plan will be posted on the NIAMS Web Site in the next 2 weeks.

XI. CONSIDERATION OF APPLICATIONS

The Council reviewed a total of 722 applications in closed session requesting $225,753,097 and recommended for $224,137,636.

XII. ADJOURNMENT

The 59th National Arthritis and Musculoskeletal and Skin Diseases Advisory Council Meeting was adjourned at 4:00 p.m. Proceedings of the public portion of this meeting are recorded in this summary.

I hereby certify that, to the best of my knowledge, the foregoing summary and attachments are accurate and complete.

Cheryl A. Kitt, Ph.D.
Executive Secretary, National Arthritis and Musculoskeletal and Skin Diseases Advisory Council

Director, Extramural Program
National Institute of Arthritis and Musculoskeletal and Skin Diseases

Stephen I. Katz, M.D., Ph.D.
Chairman, National Arthritis and Musculoskeletal and Skin Diseases Advisory Council

Director, National Institute of Arthritis and Musculoskeletal and Skin Diseases